**Extracorporeal carbon dioxide removal for patients with acute respiratory failure secondary to acute hypoxaemic respiratory failure: a systematic review and meta-analysis.**

**Review Protocol**

2021-02-05

Version 1.0

POSPERO ID []

**1. Review title**

Extracorporeal carbon dioxide removal for patients with acute respiratory failure secondary to acute hypoxaemic respiratory failure: a systematic review and meta-analysis.

**2. Anticipated start date**

2020-11-23

**3. Anticipated completion date**

2021-02-28

**4. Review team**

Jonathan Millar (University of Edinburgh); Andrew Boyle (Queen’s University Belfast); Bronagh Blackwood (Queen’s University Belfast); Claire Adams (University of Edinburgh); Tom Drake (University of Edinburgh); James McNamee (Queen’s University Belfast); Daniel McAuley (Queen’s University Belfast).

**5. Review question**

In adults (aged ≥ 18 years) with acute hypoxaemic respiratory failure (AHRF), is the use of extracorporeal carbon dioxide removal (ECCO2R) compared to conventional management, associated with an improvement in clinically important outcomes?

**6. Search sources**

*Electronic searches*

We will conduct a comprehensive search, without language restriction, including:   
- MEDLINE via PubMed (1994 – current)

- Embase (1994 – current)

We will search the following clinical trials registries for ongoing or recently completed trials:

- US NIH Ongoing Trials Register (ClinicalTrials.gov)

- WHO International Clinical Trials Registry Platform (WHO ICTRP)

- ISRCTN registry

*Other searches*

We will manually review the reference lists of all included studies for relevant articles not identified in the primary search.

**7. Search strategy**

A comprehensive search strategy was designed by an expert biomedical informatician. Search terms are specified in APPENDIX A.

**8. Types of study being included**

We will include randomised (or quasi-randomised) trials, matched cohort studies, and observational studies with a clearly stated hypothesis. We will exclude observational studies lacking a hypothesis and with 10 or fewer patients.

**9. Condition being studied**

Acute hypoxaemic respiratory failure, including Acute Respiratory Distress Syndrome (ARDS).

**10. Population**

*-- Inclusion criteria*

Any language.

Adults (aged ≥ 18 years).

AHRF of any cause.

Use of ECCO2R, veno-venous or veno-arterial.

Co-interventions in addition to ECCO2R or mechanical ventilation (in the control group) will be permitted. *-- Exclusion criteria*

Children (aged < 18 years).

Studies evaluating patients with chronic respiratory failure.

Studies evaluating patients with hypercarbic respiratory failure.

Studies employing extracorporeal membrane oxygenation (ECMO).

Studies published prior to 1st January 1994

**11. Intervention**

Extracorporeal carbon dioxide removal (ECCO2R).

**12. Control**

Conventional management.

**13. Main outcome**

Pooled 28-day mortality (intention-to-treat) across randomised controlled trials.

**13.a. Measures of effect**

If 28-day mortality is not reported, we will extrapolate on the basis of available data (survival curves or CONSORT diagrams) or substitute the closest common mortality timepoint.

**14. Additional outcomes**

*Randomised controlled trials only*

- 28-day mortality (as treated).

- 28-day mortality (per protocol).

- Mortality at longest available follow-up (intention-to-treat).

- Ventilator-free days (VFDs) at day 28.

*For observational studies and studies with matched controls*

- 28-day mortality (as treated).

- Ventilator-free days (VFDs) at day 28.

*All studies*

- Pooled 28-day mortality across randomised controlled trials and observational studies with matched control groups.

- Serious adverse events (SAEs) – all as defined by trialists.

a. Major haemorrhage (intracerebral and extracerebral).

b. Complications associated with cannulation or the ECCO2R circuit.

- Quantification of CO2 removal (latest reported value until day 3).

- Change in tidal volume (latest reported value until day 3).

- Change in minute volume (latest reported value until day 3).

- Change in pH (latest reported value until day 3).

- Change in plateau pressure (latest reported value until day 3).

**15. Data extraction**

*Selection of studies*

Article titles and abstracts obtained using the search strategy will be stored using reference management software (Endnote X9, Clarivate Analytics, United States). Initial screening against eligibility criteria will be performed by two authors independently. Inconsistencies will be resolved by discussion or reference to a third reviewer. Full text articles will be retrieved for studies matching the eligibility criteria.

*Data extraction*

Data will be extracted by two independent reviewers using a pre-piloted proforma (APPENDIX B). Inconsistencies will be resolved by discussion or reference to a third reviewer.

**16. Risk of bias**

All randomised studies will be assessed for internal validity and risk of bias using domain-based evaluation as described in the Cochrane Handbook for Systematic Reviews of Interventions, Chapter 8, version 5.0.2 (Higgins 2009). The risk of bias form extracted from Chapter 8.5.1 will be used to evaluate each included study. Each study will be assessed as low, high or uncertain risk for the adequacy of sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other bias.

All non-randomised studies will be assessed using the Cochrane Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool (Sterne 2016). Each study will be assessed as low, moderate, serious, or critical risk of bias, where there is sufficient information, for each domain and overall.

**17. Strategy for synthesis**

*Publication bias*

Publication bias will be examined visually using funnel plots.

*Heterogeneity*

For all included studies, clinical heterogeneity across study populations will be evaluated by comparing the study inclusion criteria, age, comorbidities, year of publication and origin of patients recruited to the study. Where appropriate studies with a low level of clinical heterogeneity will be pooled using meta-analysis techniques as detailed below. Statistical heterogeneity will be measured using the I2 value, where 0% to 40%: might not be important, 0% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity, 75% to 100%: considerable heterogeneity.

*Statistical Analysis*

Where at least two studies report the same outcome measure and contain low levels of clinical heterogeneity, we will pool the effect sizes using the relevant Bayesian meta-analysis model framework. For analyses where 3 studies or fewer are available for analysis, or the event in question is rare (<5% incidence in both treatment groups) we will use a fixed effects model. Where there are 4 or more studies or heterogeneity is over 50% (as measured by I2) we will use a random-effects model. We will use two approaches, the first pooling effects based with uniformed priors and the second where weakly informative priors are used. Weakly informative priors will be derived from observational studies, then subsequently combined with randomised controlled trials. We will use the half-cauchy distribution to generate weakly informative priors. We will also conduct a sequential analysis where we update each weakly informative effect prior (mu) with every study that is included in a chronological fashion. For the heterogeneity prior, tau, we will conduct analyses with tau set first at 0.2, then to the value of I2 and finally conduct sensitivity analyses by varying the value of tau between 0 and 2.0. Meta-analysis will be performed using R version 3.6.6 using the rstan and rjags program with the bayesmeta, rstan, rjags and brms packages. Pooled effect estimates, based on the posterior distribution, for binary outcomes will be presented as odds ratios, alongside the 95% credible interval. For continuous outcomes, the standardised or weighted mean difference will be used. Survival or time-to-event data will be presented as hazards ratios.

Where data are missing, we will perform a worst-best case analysis to identify whether the missing data are likely to substantially alter the size or direction of the pooled effects.

*Trial sequential analysis*

To identify whether the required information size has been met, for each outcome we will perform a trial sequential analysis.

**18. Analysis of subgroups**

The following sub-group analyses are anticipated:

* Studies including patients with ARDS
* Studies including patients with a PaO2/FiO2 ratio <150 mmHg
* Studies evaluating veno-venous ECCO2R

*Risk of bias*

We will conduct subgroup analyses to identify the impact of potential sources of bias on effect estimates by excluding studies with a high risk of bias and a high or moderate risk of bias, as identified by the Cochrane Risk Of Bias tools.

*By study design*

We will conduct prespecified analyses where we will exclude observational studies and pool randomised controlled trials only.